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Il Geriatra e la cura della Demenza

11 Novembre 2017

Aula Magna Clinica Mangiagalli Fondazione I.R.C.C.S. Ca' Granda
Ospedale Maggiore Policlinico Via Commenda 12 Milano

Supplementi nutrizionali e malattia di Alzheimer: uno spazio reale di trattamento?

Gruppo di ricerca geriatrica

ISTITUTO CLINICO S.ANNA

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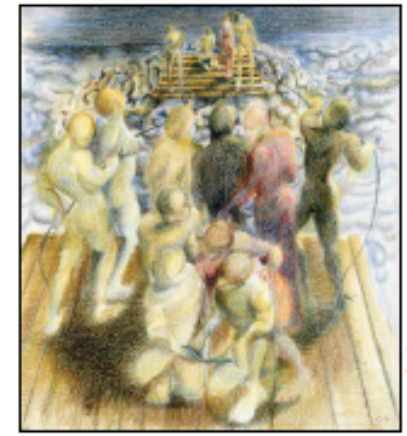
Finding a cure for Alzheimer's disease starts with prevention

The most recent Alzheimer's Association report affirms that there are more than 5 million patients with dementia in the USA, and that the disease kills more people than do prostate and breast cancers combined. According to *The Lancet Neurology* Commission on Alzheimer's disease and other dementias, "an effective therapy is perhaps the greatest unmet need facing modern medicine". It is therefore imperative that research funders set the right priorities to find a cure, and thereby align the goals of the research community with those of society. Yet, the focus of much current research is on the preclinical states of neurodegeneration and on developing interventions to prevent clinical symptoms, rather than on addressing unmet clinical needs. This emphasis on prevention, which might seem paradoxical at best or unethical at worst, is however a judicious decision.

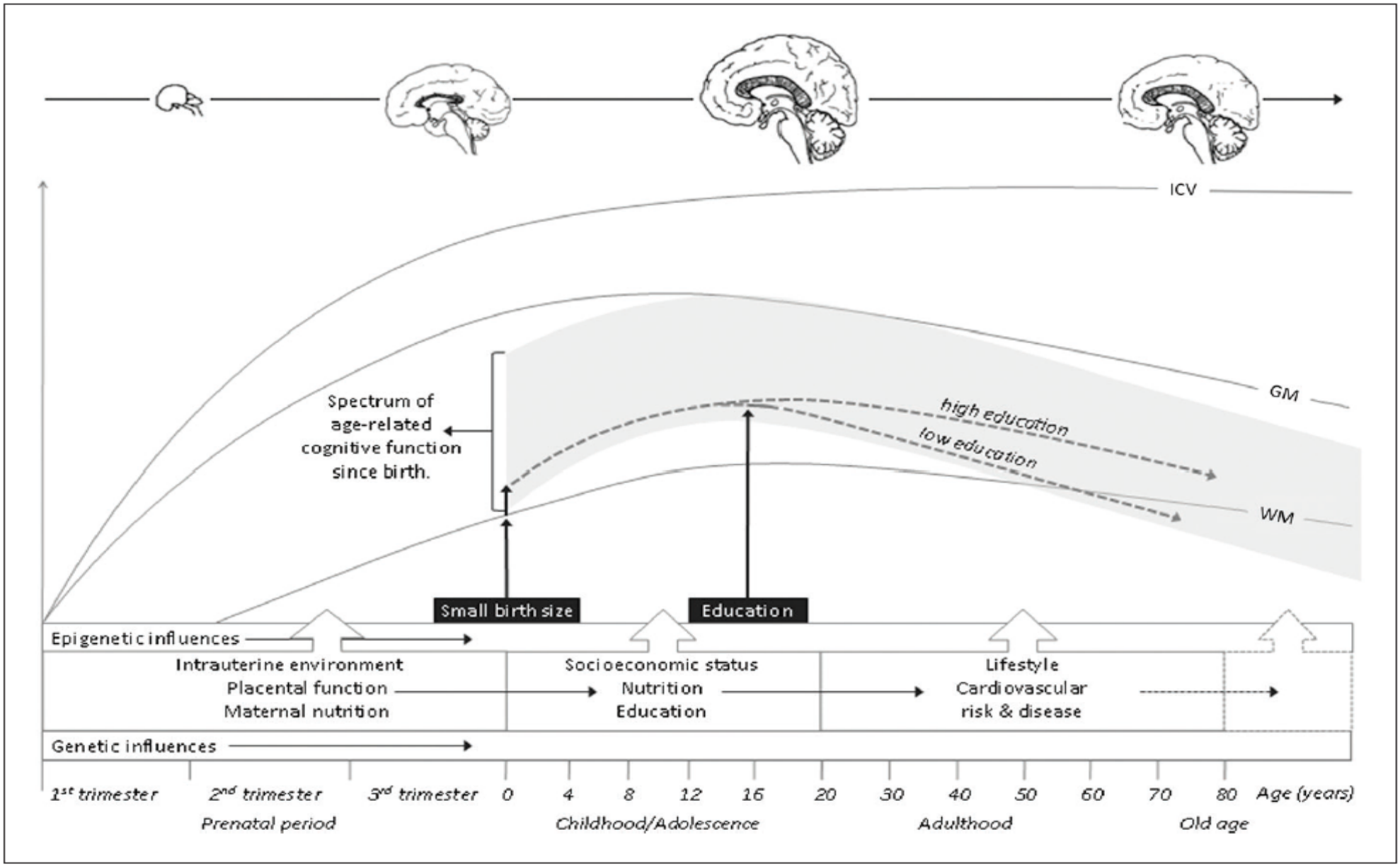


Carmelo Serrano

See Commission *Lancet Neurol* 2016; **15:** 455–532

For the **Alzheimer's Association report** see http://www.alz.org/facts/

Hypothesized model of the origins and life course of brain aging – From Muller M et al. 2014



Dementia prevention, intervention, and care

Gill Livingston, Andrew Sommerlad, Vasiliki Orgeta, Sergi G Costafreda, Jonathan Huntley, David Ames, Clive Ballard, Sube Banerjee, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Eric B Larson, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

Published online July 20, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31363-6

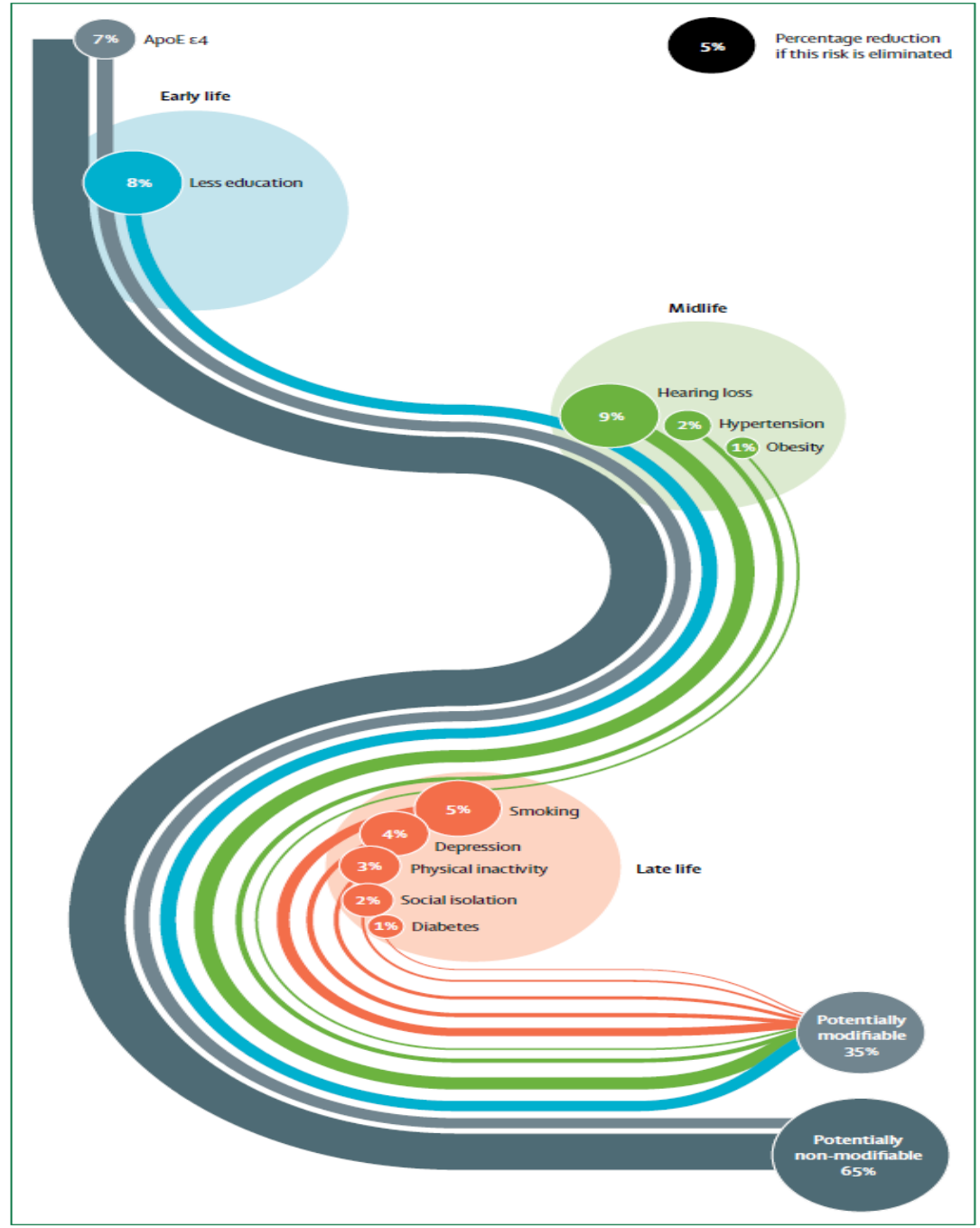


Figure 4: **Life-course model of contribution of modifiable risk factors to dementia**
Numbers are rounded to nearest integer. Figure shows potentially modifiable or non-modifiable risk factors.

Published online July 20, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31363-6

Dementia prevention, intervention, and care

Gill Livingston, Andrew Sommerlad, Vasiliki Orgeta, Sergi G Costafreda, Jonathan Huntley, David Ames, Clive Ballard, Sube Banerjee, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Eric B Larson, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

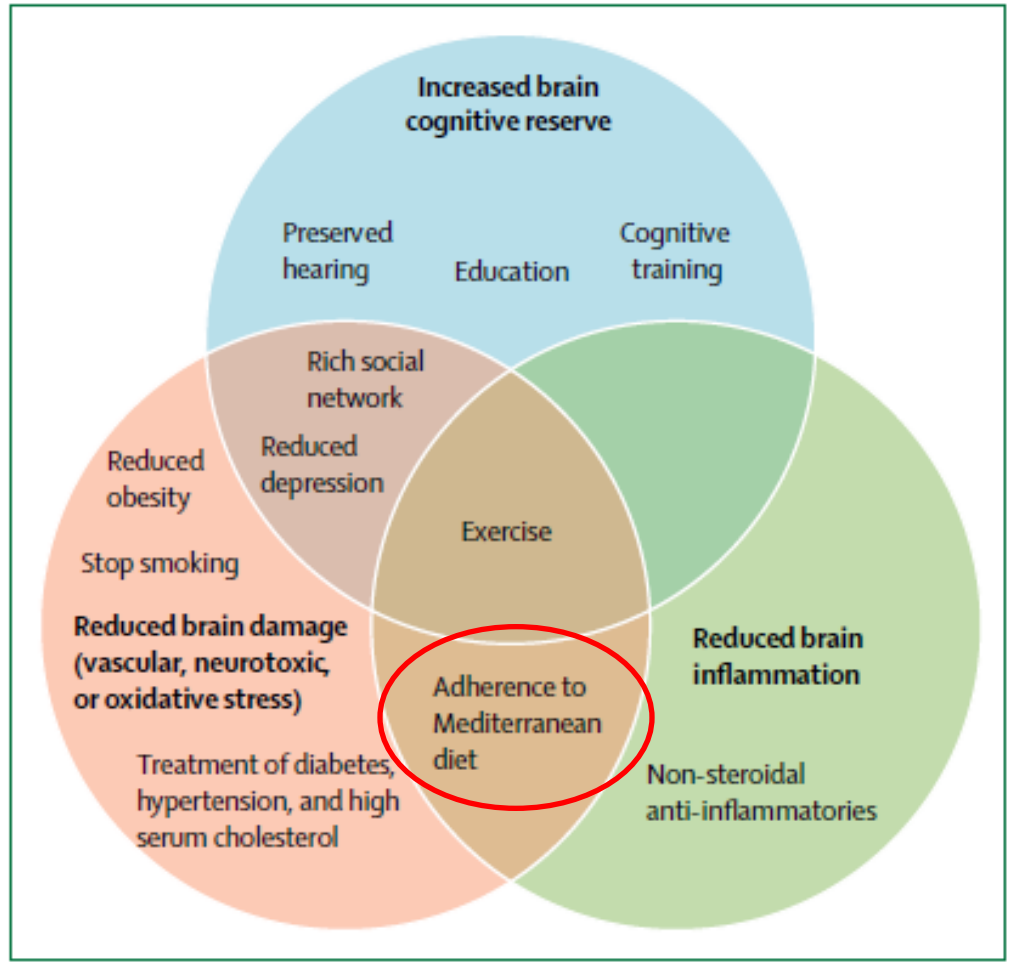


Figure 5: **Potential brain mechanisms for preventive strategies in dementia**

Nutritional factors influence cognitive functions, dementia/AD risk in elderly.

- Observational studies have shown a positive association between dietary contents, nutritional factors and risk of cognitive decline leading to dementia:
  - high intake of vitamin C and vitamin E was associated with lower risk of Alzheimer disease (RR 0.82) *(Engelhart et al, JAMA 2002)* and increasing consumption of fruits and vegetables reduce the 7 years risk to develop AD *(Ritchie et al, BMJ 2010)*
  - higher intakes of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, and dark and green leafy vegetables are associated to lower AD risk (RR 0.62 for 4 years follow-up) *(Gu et al, Arch Neurol. 2010)*
  - Increased consumption of antioxidant-rich foods in general and of polyphenols in particular (Mediterranean diet) is associated with better cognitive performance in elderly *(Valls-Pedret et al, JAD 2012)* and lower risk to develop AD and MCI *(Scarmeas et al, Ann Neurol 2006; Scarmeas et al, Arch Neurol 2009)*
  - Higher vitamin D dietary intake was associated with a lower risk of developing AD among older women (OR 0.23) in a 7-years follow-up study *(Annweiler C et al, J Gerontol 2012)*

The effect of supplementation of nutrient on cognitive function and dementia/AD risk: contrasting results

Author	Journal		Nutrient	#Subjects/ Duration	Outcome
Aisen 2008	JAMA		B-vitamins	409 18 months	This regimen of high-dose B vitamin supplements does **not slow cognitive decline** in individuals with mild to moderate AD.
Durga 2007	Lancet		Folic acid	818 36 months	Folic acid supplementation **significantly improved domains of cognitive function** in 50-70 years old not demented
McMahon 2006	NEJM		B-vitamins	276 24 months	**No significant differences** between the vitamin and placebo groups **in the scores on tests of cognition** in over 65 years old not demented.
Freund-Levi 2006	Arch Neurol		n3 PUFAs	174 6 months	Administration of n3PUFA in mild -moderate AD patients did **not delay the rate of cognitive decline** according to the MMSE or the cognitive portion of the ADAS.
Petersen 2005	NEJM		Vitamin E	769 36 months	Vitamin E had **no benefit in patients with mild cognitive impairment**.
Dysken 2014	JAMA		Vitamin E	561 2.2 years	Among patients with mild to moderate AD vitamin E compared with placebo resulted in **slower functional decline, but no improvement in cognitive function** (in combination or not wit memantine).

The effect of supplementation of nutrient on cognitive function and dementia/AD risk: contrasting results

Author	Journal		Nutrient	#Subjects/ Duration	Outcome
Quinn 2010	JAMA		DHA	402 18 months	DHA compared with placebo **did not slow the rate of cognitive and functional decline** in mild-moderate AD patients.
DeKosky 2008	JAMA		Ginkgo biloba	3069 median f-up 6.1 Y	Ginkgo biloba at 120 mg twice a day was **not effective in reducing either the overall incidence rate of dementia or AD incidence** in elderly individuals with normal cognition or those with MCI.
Stein 2011	J Alz Disease		Vitamin D2	32 8 weeks	We conclude that high-dose vitamin D provides **no benefit for cognition** or disability over low-dose vitamin D in mild-moderate AD
Rossom 2012	JAGS		Calcium and vitamin D	71 7.8 years	There were **no significant differences in incident dementia or MCI or in global or domain-specific cognitive function** between treatments groups.
Annweiler 2012	Cogn Behav Neurol		Vitamin D and memantine	43 6 months	Patients with AD who took memantine plus vitamin D had a statistically and clinically relevant **gain in cognition**,

JAMA Neurology | Original Investigation

Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE)

Richard J. Kryscio, PhD; Erin L. Abner, PhD; Allison Caban-Holt, PhD; Mark Lovell, PhD; Phyllis Goodman, MS; Amy K. Darke, MS; Monica Yee, BA; John Crowley, PhD; Frederick A. Schmitt, PhD

JAMA Neurol. doi:10.1001/jamaneurol.2016.5778
Published online March 20, 2017.

IMPORTANCE Oxidative stress is an established dementia pathway, but it is unknown if the use of antioxidant supplements can prevent dementia.

OBJECTIVE To determine if antioxidant supplements (vitamin E or selenium) used alone or in combination can prevent dementia in asymptomatic older men.

DESIGN, SETTING, AND PARTICIPANTS The Prevention of Alzheimer's Disease by Vitamin E and Selenium (PREADViSE) trial began as a double-blind randomized clinical trial in May 2002, which transformed into a cohort study from September 2009 to May 2015. The PREADViSE trial was ancillary to the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a randomized clinical trial of the same antioxidant supplements for preventing prostate cancer, which closed in 2009 owing to findings from a futility analysis. The PREADViSE trial recruited 7540 men, of whom 3786 continued into the cohort study. Participants were at least 60 years old at study entry and were enrolled at 130 SELECT sites, and Cox proportional hazards models were used in a modified intent-to-treat analysis to compare hazard rates among the study arms.

INTERVENTIONS Participants were randomized to vitamin E, selenium, vitamin E and selenium, or placebo. While taking study supplements, enrolled men visited their SELECT site and were evaluated for dementia using a 2-stage screen. During the cohort study, men were contacted by telephone and assessed using an enhanced 2-stage cognitive screen. In both phases, men were encouraged to visit their physician if the screen results indicated possible cognitive impairment.

MAIN OUTCOMES AND MEASURES Dementia case ascertainment relied on a consensus review of the cognitive screens and medical records for men with suspected dementia who visited their physician for an evaluation or by review of all available information, including a functional assessment screen.

RESULTS The mean (SD) baseline age of the 7540 participants was 67.5 (5.3) years, with 3936 (52.2%) reporting a college education or better, 754 (10.0%) reporting black race, and 505 (6.7%) reporting Hispanic ethnicity. Dementia incidence (325 of 7338 men [4.4%]) was not different among the 4 study arms. A Cox model, which adjusted incidence for participant demographic information and baseline self-reported comorbidities, yielded hazard ratios of 0.88 (95% CI, 0.64-1.20) for vitamin E, 0.83 (0.60-1.13) for selenium, and 1.00 (0.75-1.35) for the combination compared with placebo.

CONCLUSIONS AND RELEVANCE Neither supplement prevented dementia. To our knowledge, this is the first study to investigate the long-term association of antioxidant supplement use and dementia incidence among asymptomatic men.

Table 1. Randomized Clinical Trials of ω-3 Supplementation and Cognitive Outcomes

Source by Study Condition	Mean Age, y	Intervention	Duration	Outcomes	No. of Participants	Comments
Alzheimer disease						
Quinn et al,[13] 2010	76	2 g/d of DHA vs placebo	18 mo	Cognitive tests	384	No overall effect
Freund-Levi et al,[14] 2006	73	1.7 g/d of DHA and 0.6 g/d of EPA vs placebo	12 mo	Cognitive tests	204	No overall effect
Mild cognitive impairment						
van de Rest et al,[15] 2008	70	1800 mg/d of EPA-DHA and 400 mg/d of EPA-DHA vs placebo	6 mo	Cognitive tests	302	No overall effect
Chiu et al,[16] 2008	75	1080 mg/d of EPA and 720 mg/d of DHA vs placebo	24 mo	Cognitive tests	30	No overall effect. Among participants with MMSE score >27, improved cognition scores
Lee et al,[17] 2013	65	430 mg/d of DHA and 150 mg/d of EPA vs placebo	12 mo	Cognitive tests	36	Improved short-term and working memory
Sinn et al,[18] 2012	74	EPA (1.67 g/d EPA + 0.16 g/d DHA), DHA (1.55 g/d of DHA + 0.40 g/d of EPA) or linoleic acid (2.2 g/d)	6 mo	GDS and cognitive tests	54	Verbal fluency improved in the DHA group
Cognitively healthy						
Stonehouse et al,[19] 2013	33	1.16 g/d of DHA vs placebo	6 mo	Cognitive tests	176	Improved memory retention times
Külzow et al,[20] 2016	50-75	2200mg/d ofDHAand EPA vsplacebo	6 mo	Memory outcomes	44	Cued recall was significantly better after ω-3 supplementation
Benton et al,[21] 2013	22	400 mg/d of DHA vs placebo	50 d	Memory outcomes	285	No effect on cognitive scores
Jackson et al,[22] 2012	22	1 g/d of DHA or 1 g/d of EPA vs placebo	12 wk	Cognitive tests	159	No effect on cognitive scores
Yurko-Mauro et al,[23] 2010	70	900 mg/d of DHA vs placebo	6 mo	Memory outcomes	485	Improved learning and memory function
Johnson et al,[24] 2008	68	800 mg/d of DHA vs placebo	4 mo	Memory outcomes	20	Improved verbal fluency scores
Danghour et al,[25] 2010	75	200 mg/d of EPA plus 500 mg/d of DHA vs placebo	24 mo	Memory outcomes	867	Cognitive function did not decline in either study arm for duration
Geleijnse et al,[26] 2012	69	400 mg/d of EPA-DHA vs placebo	40 mo	Global cognition	1265	No effect of dietary doses of ω-3 fatty acids on global cognitive decline

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GDS, Geriatric Depression scale; MMSE, Mini-Mental State Examination.

EDITORIAL

Preventing Dementia

Many Issues and Not Enough Time

Steven T. DeKosky, MD; Lon S. Schneider, MD

JAMA Neurology Published online March 20, 2017

The PREADViSE trial illustrates many of the difficulties for undertaking prevention trials: uncertainty of medication dose, mechanisms of action, and proof of target engagement; proper selection of a diverse population that can be observed for a realistic period to yield enough cases of dementia to determine success or failure of the intervention; use of appropriate assessment tools and methods of accurate diagnosis; and use of effective ways for maintaining participation and assuring adherence in the study over time. The research team addressed these issues as well as they could, especially considering it was an add-on study. Finding efficient and cost-saving ways to address these issues in long-term, disease-modifying trials must be major goals for research groups around the world.

AD Risk and combination of nutrients

Observational studies suggest a link between Mediterranean diet & AD risk

<u>Mediterranean diet:</u>

- High vegetables, legumes, fruits, and cereals
- High unsaturated fatty acids
- Low saturated fatty acids
- Moderately high fish
- Low-to-moderate dairy
- Low meat and poultry
- Regular but moderate amount of ethanol, primarily in the form of wine and generally, during meals

Scarmeas et al, Ann Neurol, 2006; Psaltopoulou et al, Public Health Nutr, 2008;
Feart et al, JAMA, 2009; Cherbuin et al, Am J Geriatr Psychiatry, 2011; Tangney et al, Am J Clin Nutr, 2011

Mediterranean Diet and Age-Related Cognitive Decline
A Randomized Clinical Trial

Cinta Valls-Pedret, MSc; Aleix Sala-Vila, DPharm, PhD; Mercè Serra-Mir, RD; Dolores Corella, DPharm, PhD; Rafael de la Torre, DPharm, PhD; Miguel Ángel Martínez-González, MD, PhD; Elena H. Martínez-Lapiscina, MD, PhD; Montserrat Fitó, MD, PhD; Ana Pérez-Heras, RD; Jordi Salas-Salvadó, MD, PhD; Ramon Estruch, MD, PhD; Emilio Ros, MD, PhD

IMPORTANCE Oxidative stress and vascular impairment are believed to partly mediate age-related cognitive decline, a strong risk factor for development of dementia. Epidemiologic studies suggest that a Mediterranean diet, an antioxidant-rich cardioprotective dietary pattern, delays cognitive decline, but clinical trial evidence is lacking.

OBJECTIVE To investigate whether a Mediterranean diet supplemented with antioxidant-rich foods influences cognitive function compared with a control diet.

DESIGN, SETTING, AND PARTICIPANTS Parallel-group randomized clinical trial of 447 cognitively healthy volunteers from Barcelona, Spain (233 women [52.1%]; mean age, 66.9 years), at high cardiovascular risk were enrolled into the Prevención con Dieta Mediterránea nutrition intervention trial from October 1, 2003, through December 31, 2009. All patients underwent neuropsychological assessment at inclusion and were offered retesting at the end of the study.

INTERVENTIONS Participants were randomly assigned to a Mediterranean diet supplemented with extravirgin olive oil (1 L/wk), a Mediterranean diet supplemented with mixed nuts (30 g/d), or a control diet (advice to reduce dietary fat).

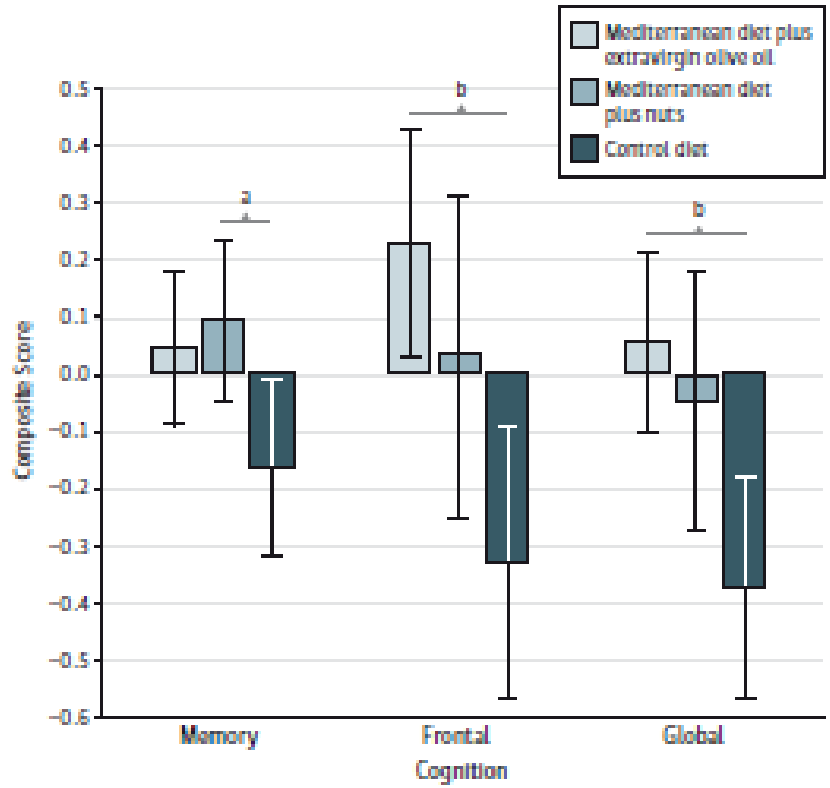
MAIN OUTCOMES AND MEASURES Rates of cognitive change over time based on a neuropsychological test battery: Mini-Mental State Examination, Rey Auditory Verbal Learning Test (RAVLT), Animals Semantic Fluency, Digit Span subtest from the Wechsler Adult Intelligence Scale, Verbal Paired Associates from the Wechsler Memory Scale, and the Color Trail Test. We used mean *z* scores of change in each test to construct 3 cognitive composites: memory, frontal (attention and executive function), and global.

RESULTS Follow-up cognitive tests were available in 334 participants after intervention (median, 4.1 years). In multivariate analyses adjusted for confounders, participants allocated to a Mediterranean diet plus olive oil scored better on the RAVLT ($P = .049$) and Color Trail Test part 2 ($P = .04$) compared with controls; no between-group differences were observed for the other cognitive tests. Similarly adjusted cognitive composites (mean *z* scores with 95% CIs) for changes above baseline of the memory composite were 0.04 (−0.09 to 0.18) for the Mediterranean diet plus olive oil, 0.09 (−0.05 to 0.23; $P = .04$ vs controls) for the Mediterranean diet plus nuts, and −0.17 (−0.32 to −0.01) for the control diet. Respective changes from baseline of the frontal cognition composite were 0.23 (0.03 to 0.43; $P = .003$ vs controls), 0.03 (−0.25 to 0.31), and −0.33 (−0.57 to −0.09). Changes from baseline of the global cognition composite were 0.05 (−0.11 to 0.21; $P = .005$ vs controls) for the Mediterranean diet plus olive oil, −0.05 (−0.27 to 0.18) for the Mediterranean diet plus nuts, and −0.38 (−0.57 to −0.18) for the control diet. All cognitive composites significantly ($P < .05$) decreased from baseline in controls.

CONCLUSIONS AND RELEVANCE In an older population, a Mediterranean diet supplemented with olive oil or nuts is associated with improved cognitive function.

JAMA Intern Med. 2015;175(7):1094-1103. doi:10.1001/jamainternmed.2015.1668
Published online May 11, 2015.

Figure 2. Changes in Cognitive Function Measured With Composites by Intervention Group



Error bars indicate 95% CIs. *P* values by analysis of covariance were adjusted for sex, baseline age, years of education, marital status, *APOE* ε4 genotype, ever smoking, baseline body mass index, energy intake, physical activity, type 2 diabetes mellitus, hyperlipidemia, ratio of total cholesterol to high-density lipoprotein cholesterol, statin treatment, hypertension, use of anticholinergic drugs, and time of follow-up, with the Bonferroni post hoc test. For each cognitive composite, the changes between the 2 Mediterranean arms were not statistically different ($P > .99$ for all). The changes for memory between the Mediterranean diet plus olive oil and control groups and for frontal and global cognition between the Mediterranean diet plus nuts and control groups had values of $P < .25$.

[a] $p < .05$.

[b] $p < .01$.

Mediterranean diet and brain structure in a multiethnic elderly cohort

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ABSTRACT

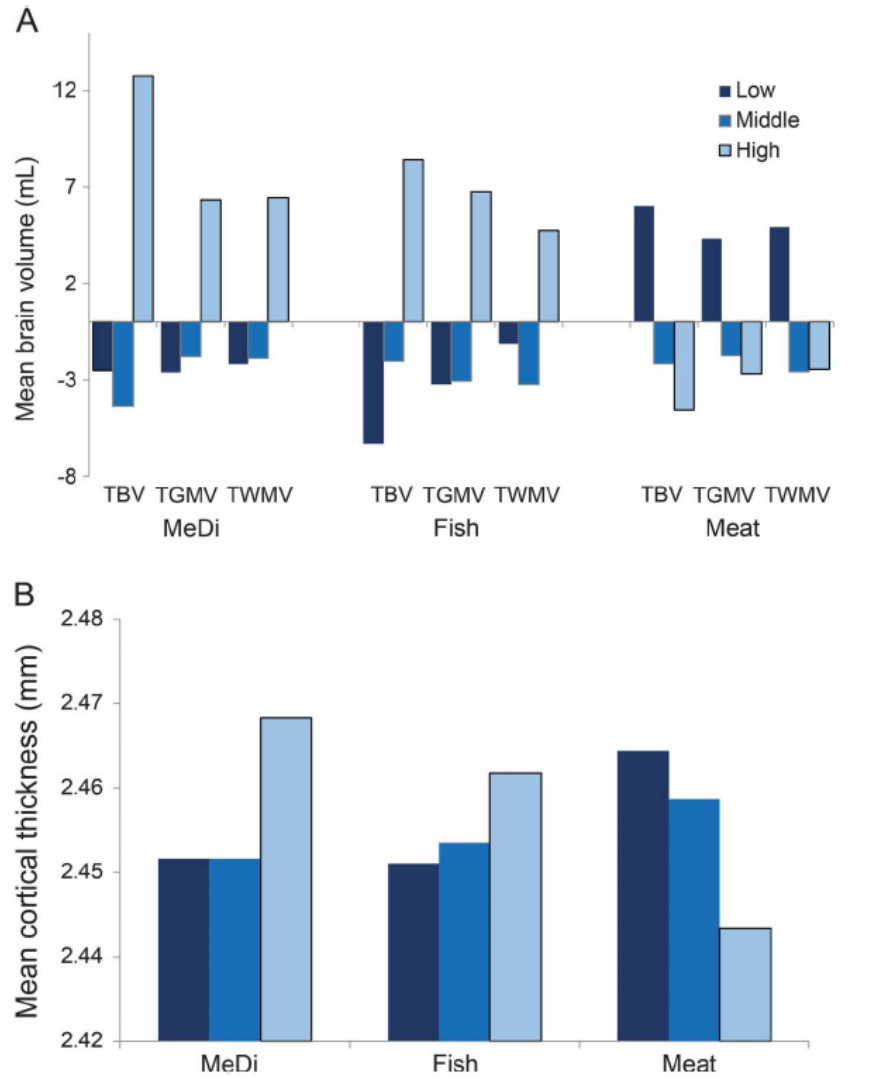
Objective: To determine whether higher adherence to a Mediterranean-type diet (MeDi) is related with larger MRI-measured brain volume or cortical thickness.

Methods: In this cross-sectional study, high-resolution structural MRI was collected on 674 elderly (mean age 80.1 years) adults without dementia who participated in a community-based, multiethnic cohort. Dietary information was collected via a food frequency questionnaire. Total brain volume (TBV), total gray matter volume (TGMV), total white matter volume (TWMV), mean cortical thickness (mCT), and regional volume or CT were derived from MRI scans using FreeSurfer program. We examined the association of MeDi (scored as 0–9) and individual food groups with brain volume and thickness using regression models adjusted for age, sex, ethnicity, education, body mass index, diabetes, and cognition.

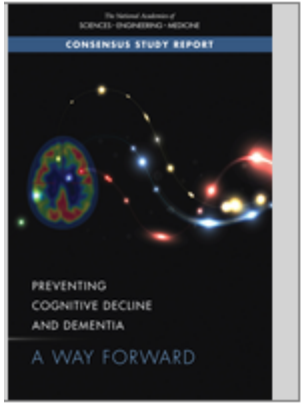
Results: Compared to lower MeDi adherence (0–4), higher adherence (5–9) was associated with 13.11 ($p = 0.007$), 5.00 ($p = 0.05$), and 6.41 ($p = 0.05$) milliliter larger TBV, TGMV, and TWMV, respectively. Higher fish (b = 7.06, $p = 0.006$) and lower meat (b = 8.42, $p = 0.002$) intakes were associated with larger TGMV. Lower meat intake was also associated with larger TBV (b = 12.20, $p = 0.02$). Higher fish intake was associated with 0.019 mm ($p = 0.03$) larger mCT. Volumes of cingulate cortex, parietal lobe, temporal lobe, and hippocampus and CT of the superior-frontal region were associated with the dietary factors.

Conclusions: Among older adults, MeDi adherence was associated with less brain atrophy, with an effect similar to 5 years of aging. Higher fish and lower meat intake might be the 2 key food elements that contribute to the benefits of MeDi on brain structure. *Neurology*® 2015;85:1744–1751

Figure Association of Mediterranean diet, fish, and meat with brain volume and cortical thickness



(A) Mean levels (intracranial-adjusted residuals) of total brain volume (TBV), total gray matter volume (TGMV), and total white matter volume (TWMV) among participants with low (score 0–2), middle (score 3–5), and high (score 6–9) levels of adherence to the Mediterranean diet (MeDi), among tertiles of fish consumption (caloric intake adjusted residuals), and among tertiles of meat consumption (caloric intake adjusted residuals). (B) Mean cortical thickness by levels of MeDi, fish, and meat consumption.



Preventing Cognitive Decline and Dementia

< Pre

A Way Forward

Authors: National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on Preventing Dementia and Cognitive Impairment. Editors: Autumn Downey, Clare Stroud, Story Landis, and Alan I. Leshner.

Washington (DC): National Academies Press (US); 2017 Jun 22.
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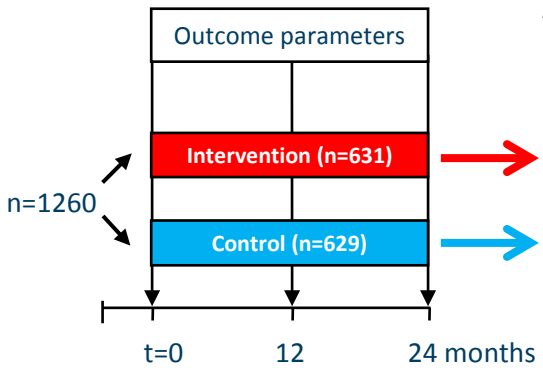
- Only cognitive training interventions were found to have positive effects (and just in the cognitive domain targeted by the intervention).
- Some, but weaker, evidence was found in support of physical activity interventions
- **Weaker evidence was found in support of nutraceutical and diet interventions.**
- The evidence on the cognitive effects of antihypertensive treatment was deemed encouraging, but inconclusive.

THE LANCET
Published online: March 11, 2015

Articles

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

Tiia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levälahti, Satu Ahtiluoto, Riitta Antikainen, Lars Bäckman, Tuomo Hänninen, Antti Jula, Tiina Laatikainen, Jaana Lindström, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Markku Peltonen, Rainer Rauramaa, Anna Stigsdotter-Neely, Timo Strandberg, Jaakko Tuomilehto, Hilkka Soininen, Miia Kivipelto



Age: 69,4
MMSE: 26,7

diet, exercise, cognitive training, vascular risk monitoring

general health advice

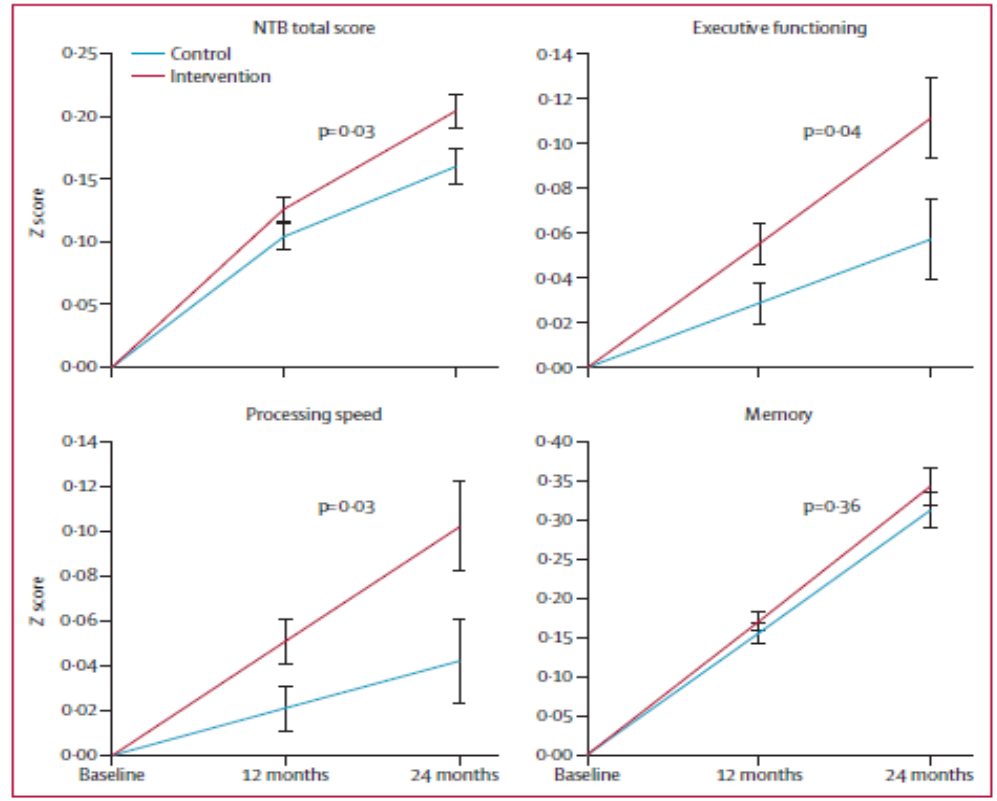


Figure 2: **Change in cognitive performance during the 2 year intervention**
Figure shows estimated mean change in cognitive performance from baseline until 12 and 24 months (higher scores suggest better performance) in the modified intention-to-treat population. Error bars are SEs. Mixed-model repeated-measures analyses were used to assess between-group differences (group x time interaction) in changes from baseline to 24 months based on data from all participants with at least one post-baseline measurement. NTB=neuropsychiatric test battery.

	FINGER[185]	MAPT[186]	PreDIVA[187]	HATICE[188]
Sample size	1260 community dwellers from previous population-based observational cohorts	1680 community dwellers	3533 community dwellers	4600 community dwellers
Main inclusion criteria	Dementia CAIDE risk score >6 and cognitive performance at the mean level or slightly lower than expected for age	Frail elderly individuals (subjective memory complaint, slow walking speed, IADL limitations)	All elderly patients without dementia in general practices	Older adults without dementia with increased risk of cardiovascular disorders and dementia
Age at enrolment	60–77 years	≥70 years	70–78 years	≥65 years
Study design	Multicentre, randomised parallel-group controlled trial	Multicentre, randomised controlled trial	Multisite, cluster-randomised parallel-group controlled trial	Multinational, multicentre, randomised parallel-group controlled trial
Intervention	Multidomain: nutritional guidance, physical activity, cognitive training, social activity, management of vascular risk factors	Multidomain: vascular care, nutritional advice, exercise advice, cognitive training with or without 800 mg docosahexaenoic acid per day	Multidomain: nurse-led vascular care, including medical treatment of risk factors, nutritional advice, exercise advice	Multidomain e-health: interactive internet platform with nurse-led support to optimise management of vascular and lifestyle-related risk factors
Duration	2 years plus 5 years' follow-up	3 years plus 2 years' follow-up	6 years	1·5 years
Outcomes	Primary: change in cognitive function Secondary: dementia, depression, disability, cardiovascular events, quality of life, health-resource use, change in AD biomarkers	Primary: change in cognitive function Secondary: cognition, functional status, depression, health-resource use, change in AD biomarkers	Primary: dementia, disability Secondary: cognitive decline, depression, cardiovascular events	Primary: optimisation of cardiovascular and dementia risk management Secondary: change in cognitive function, dementia, cardiovascular conditions, mortality, hospital admission, depression, disability, cost-effectiveness
Status	Completed in 2014	Completed in 2014	Completed in 2015	Due to finish in 2017

FINGER=Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability. MAPT=Multidomain Alzheimer Prevention Study. PreDIVA=Prevention of Dementia by Intensive Vascular Care. HATICE=Healthy Ageing Through Internet Counselling in the Elderly. CAIDE=Cardiovascular Risk Factors, Aging, and Incidence of Dementia. IADL=instrumental activities of daily living. AD=Alzheimer's disease.

Table 4: **Randomised controlled trials of multidomain interventions for prevention of cognitive impairment, dementia, or Alzheimer's disease**

Pointing the way to primary prevention of dementia

The launch of the World Wide FINGERS network—a research initiative to prevent or delay the onset of cognitive decline—on July 19, 2017, at the Alzheimer's Association International Conference (AAIC) was promising news. The risk of Alzheimer's disease (AD), the most common form of dementia, is in a large part modulated by genetics, but prevalence is decreasing in many high-income countries; hence, modifiable risk factors are also at work. Identifying and tackling these factors is an urgent research priority, for which the network is a step in the right direction.

In line with the recommendations from the NIA report and *The Lancet* Commission, the FINGER lifestyle intervention will now be adapted to, and tested in, several other countries, including China, Singapore, the USA, and the UK. By harmonising methodology and sharing data, the World Wide FINGERS network can generate robust evidence on the effectiveness of combined interventions in different settings and populations. In a few years, evidence should be available to guide public-health policies to diminish the enormous burden of dementia and its costs for health-care systems worldwide. ■ *The Lancet Neurology*

Table 4
Nutritional problems arising in different disease stages.

Nutritional problems	Stage of dementia
Olfactory and taste dysfunction	Preclinical and early stages
Attention deficit	Mild to moderate
Executive functions deficit (shopping, preparing food)	Mild to moderate
Impaired decision-making ability (slowdown in food choice, reduced intake)	Mild to moderate
Dyspraxia[a]	Moderate to severe
Agnosia[b]	Moderate to severe
Behavioral problems (wandering, agitation, disturbed eating behavior)	Moderate to severe
Oropharyngeal dysphagia	Moderate to severe
Refusal to eat	Severe

[a] Coordination disorder, loss of eating skills.
[b] Loss of ability to recognize objects or comprehend the meaning of objects, which means that food may not be distinguished from non-food and that eating utensils are not recognized as what they are.

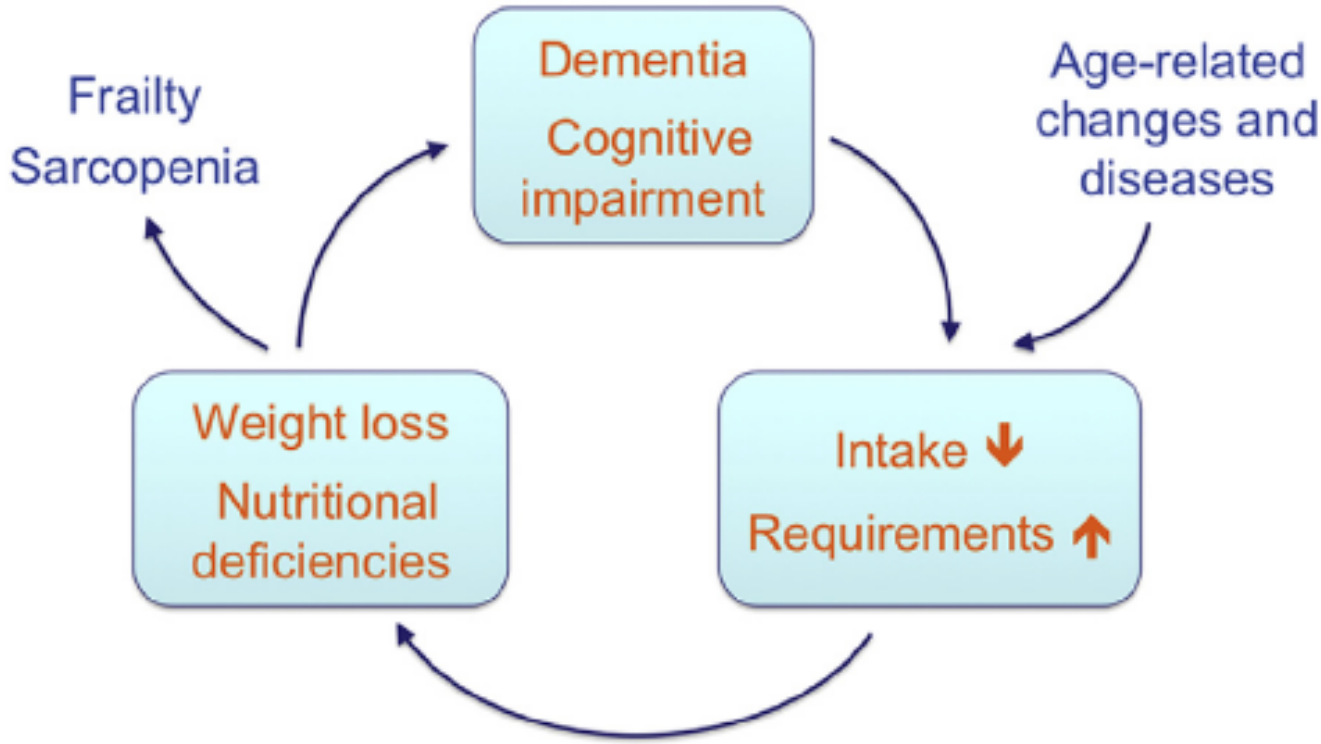


Fig. 1. Vicious circle of malnutrition and dementia.

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e-SPEN guideline

ESPEN guidelines on nutrition in dementia

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food in a pleasant environment, by adequate nursing support and elimination of potential causes of malnutrition. Supplementation of single nutrients is not recommended unless there is a sign of deficiency. Oral nutritional supplements are recommended to improve nutritional status but not to correct cognitive impairment or prevent cognitive decline. Artificial nutrition is suggested in patients with mild

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Keywords:
Guideline
Dementia
Malnutrition
Nutritional support
Nutritional interventions

nutritional problems, and the question arises which interventions are effective in maintaining adequate nutritional intake and nutritional status in the course of the disease. It is of further interest whether supplementation of energy and/or specific nutrients is able to prevent further cognitive decline or even correct cognitive impairment, and in which situations artificial nutritional support is justified.

Objective: It is the purpose of these guidelines to cover these issues with evidence-based recommendations.

Methods: The guidelines were developed by an international multidisciplinary working group in accordance with officially accepted standards. The GRADE system was used for assigning strength of evidence. Recommendations were discussed, submitted to Delphi rounds and accepted in an online survey among ESPEN members.

Results: 26 recommendations for nutritional care of older persons with dementia are given. In every person with dementia, screening for malnutrition and close monitoring of body weight are recommended. In all stages of the disease, oral nutrition may be supported by provision of adequate, attractive food in a pleasant environment, by adequate nursing support and elimination of potential causes of malnutrition. Supplementation of single nutrients is not recommended unless there is a sign of deficiency. Oral nutritional supplements are recommended to improve nutritional status but not to correct cognitive impairment or prevent cognitive decline. Artificial nutrition is suggested in patients with mild or moderate dementia for a limited period of time to overcome a crisis situation with markedly insufficient oral intake, if low nutritional intake is predominantly caused by a potentially reversible condition, but not in patients with severe dementia or in the terminal phase of life.

Conclusion: Nutritional care and support should be an integral part of dementia management. In all stages of the disease, the decision for or against nutritional interventions should be made on an individual basis after carefully balancing expected benefit and potential burden, taking the (assumed) patient will and general prognosis into account.

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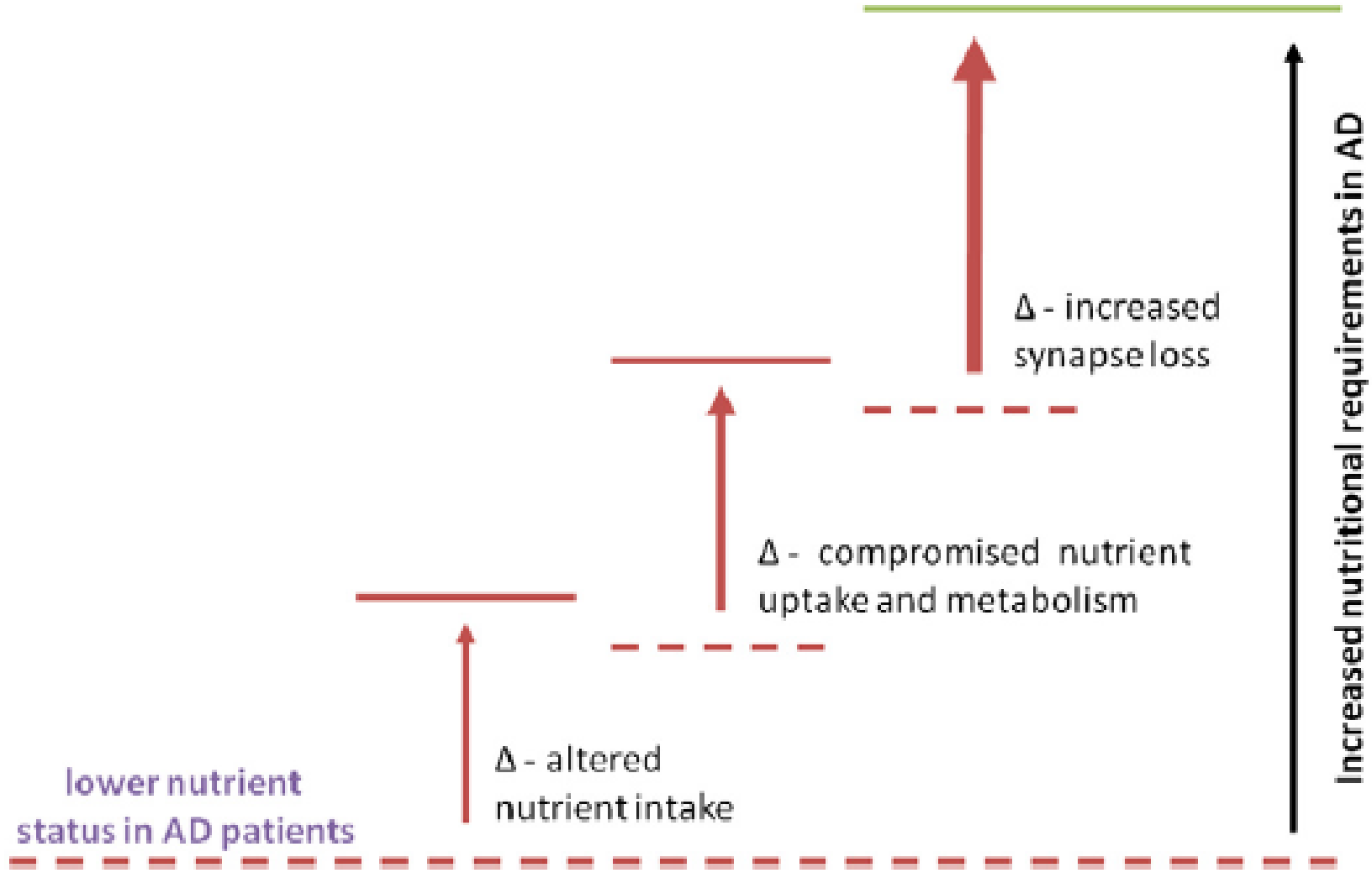
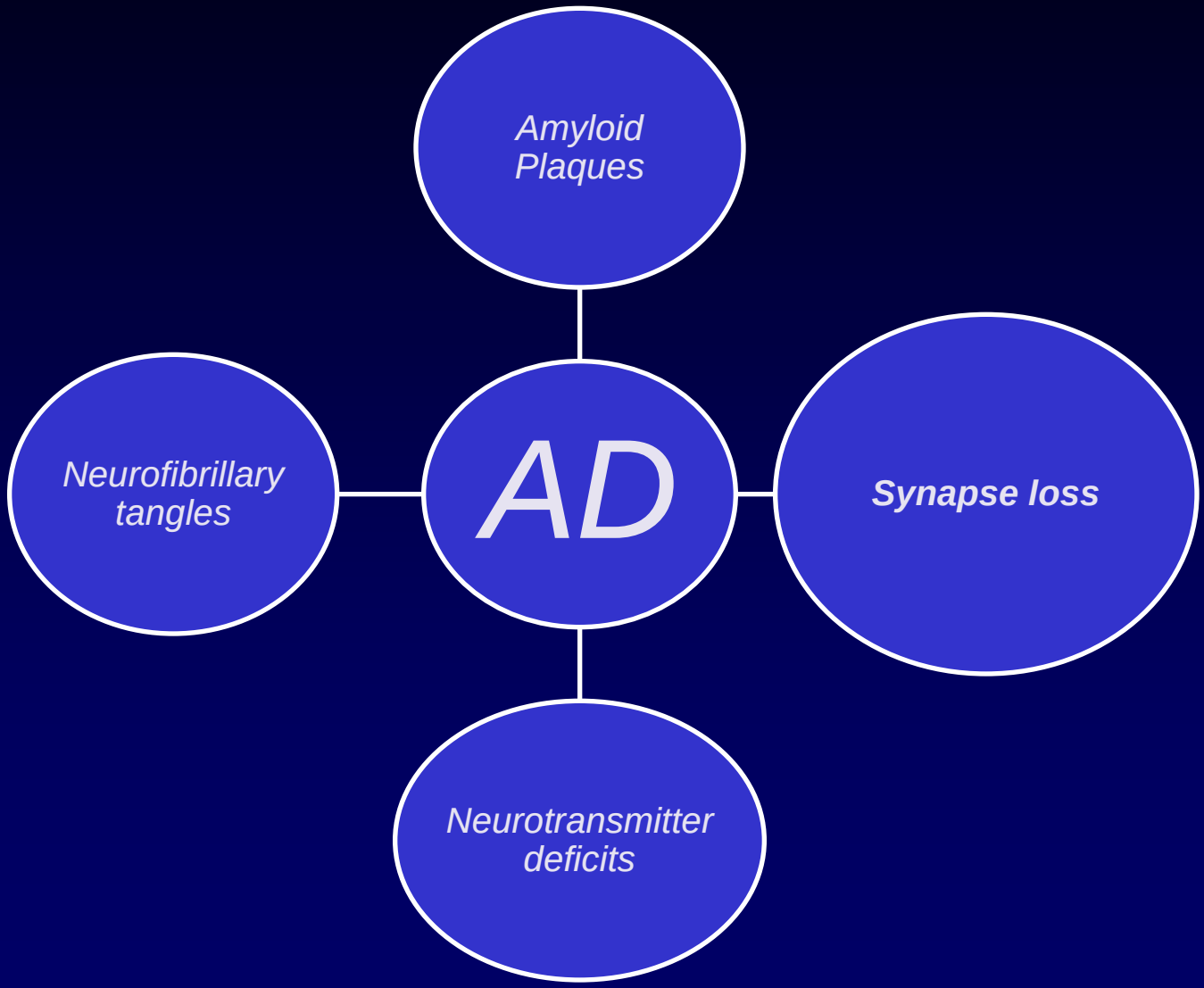
Rationale for a nutritional approaches in AD



W. Mi et al, Nutrition 2013

Intervention targets in Alzheimer's disease

Amyloid plaques*, *neurofibrillary tangles*, *synapse loss *play a central role in the pathogenesis of AD and may be intervention targets*



Nutraceutical intervention in ageing brain

JGG 2017;65:79-92

S. De Domenico[1], A.M. Giudetti[2]

Table I. Nutraceutical compounds with potential effects on age associated brain alterations.

Nutraceutical	Experimetal model	Effect	Ref.
Polyphenols			
Flavanones	Cell cultures	Neuroprotective and neuromodulator.	80
Procyanidin (pine-bark estracts)	Clinical study	Beneficial effects on oxidative stress and cognition.	77, 88
Flavonoids	Cell cultures Clinical study	Apoptosis inhibition-neuronal differentiation. Vascular blood flow promotion. ROS scavengers.	83 83 84
EGb 761 (Ginkgo biloba)	Cell cultures and clinical study	Enhances neurocognitive functions in AD and in older adults.	96, 97
Grape, pomegranate, strawberry and blueberry flavonoids	Rat and clinical study	Enhances the efficiency of memory.	93-95
Soy isoflavones	Clinical study	Improve neurocognitive function and mood in post- menopause.	102, 103
Resveratrol	Cell cultures	Anti-inflammatory effect. Therapeutic effect in PD.	107 109
Epigallochatechin-3-gallate	Epidemiological study	Decreases the incidence of neurodegenerative disorders.	117-119
Curcumin	Rat, mouse and clinical study	Anti-inflammatory and antioxidant in neurodegeneration. Inhibits formation of Aβ oligomers, fibrils, binds plaques, and reduces amyloid.	112-115 113-116

S. De Domenico[1], A.M. Giudetti[2]

JGG 2017;65:79-92

Vitamins and oligoelements			
Ascorbic acid	Cell cultures, mouse and clinical study	Antioxidant effects.	123
Vitamin E	Cell culture and animal study	Improves cognitive behaviors in rodents. Neuroprotective in apoE-deficient mice. Modifies Aβ toxicity in cultured hippocampal neurons. Improves brain mitochondrial function.	124 125 126 57
Vitamins C and E	Clinical study	Reduce AD incidence.	127
1,25(OH)2D3	Cell cultures	Inhibits TNF-α, IL-6, and nitric oxide production by the stimulated microglia.	130
Lipoic acid	Rat	Prevents mitochondria damage.	131
Zinc	Mouse Clinical study	Improves myelination. Improves brain compensatory capacity.	135 136
PUFA			
ω-3 PUFA (DHA)	Animal and clinical study	Reduce impaired cognitive functions. Protective against Aβ production and dendritic pathology in AD. Attenuate oxidative stress. Reduce Aβ and Tau accumulation. Diminish Parkinsonism symptoms and dyskinesia. Enhancing the expression of neurotrophic factors.	140-143 152-154 156,159 175-159 160, 161 162
Other compounds			
Carnosine	Cell cultures, monkeys, rat, rabbit	Antioxidant effects. Modulates MAO activity. Controls toxic effect of Aβ.	167-170 172 173-175
Creatine	Clinical study	Efficacious as a treatment in PD.	179
Acetyl-L-carnitine	Animal study	Reverses decline in mitochondrial functions. Improves clinical features of AD. Improves energy to nerve terminals.	180, 181, 183-185 181, 183 182
Taurine	Cell cultures Mouse	Ameliorates neuroinflammation. Ameliorates age-dependent decline in spatial memory.	186 187

Review

Seyed Khosrow Tayebati* and Francesco Amenta

Choline-containing phospholipids: relevance to brain functional pathways

Clin Chem Lab Med 2013; 51(3): 513–521

Abstract

Choline participates in several relevant neurochemical processes. It is the precursor and metabolite of acetylcholine (ACh), plays a role in single-carbon metabolism and is an essential component of different membrane phospholipids (PLs). PLs are structural components of cell membranes involved in intraneuronal signal transduction. This paper reviews the roles of choline and of choline-containing phospholipids (CCPLs) on brain metabolism in health and disease followed by an analysis of the effects of exogenously administered CCPLs on the brain, a topic extensively investigated by literature. Based on the observation of decreased cholinergic neurotransmission in brain disorders characterized by cognitive impairment, cholinergic precursor loading therapy with CCPLs was the first approach used to attempt for relieving the cognitive symptoms of Alzheimer's disease. This therapeutic strategy was discontinued due to the negative clinical results obtained with choline or lecithin. Negative results obtained with some compounds cannot be generalized for all CCPLs, as CDP-choline (citicoline) and to a greater extent choline alphoscerate (GPC) displayed interesting effects documented in preclinical studies and limited clinical trials. We provide evidence in favor of CDP-choline and GPC activity in cerebrovascular or neurodegenerative disorders characterized by cholinergic neurotransmission impairment. Based on the results of the controlled clinical trials available, we suggest that due to the lack of novel therapeutic strategies, safe compounds developed a long time ago such as effective CCPLs could have still a place in pharmacotherapy. Therefore selected compounds of this class should be further investigated by new appropriate clinical studies.

Long-term use of standardised ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial

*Bruno Vellas, Nicola Coley, Pierre-Jean Ousset, Gilles Berrut, Jean-François Dartigues, Bruno Dubois, Hélène Grandjean, Florence Pasquier, François Piette, Philippe Robert, Jacques Touchon, Philippe Garnier, Hélène Mathiex-Fortunet, Sandrine Andrieu, for the GuidAge Study Group**

Summary

Background Prevention strategies are urgently needed to tackle the growing burden of Alzheimer's disease. We aimed to assess efficacy of long-term use of standardised ginkgo biloba extract for the reduction of incidence of Alzheimer's disease in elderly adults with memory complaints.

Methods In the randomised, parallel-group, double-blind, placebo-controlled GuidAge clinical trial, we enrolled adults aged 70 years or older who spontaneously reported memory complaints to their primary-care physician in France. We randomly allocated participants in a 1:1 ratio according to a computer-generated sequence to a twice per day dose of 120 mg standardised ginkgo biloba extract (EGb761) or matched placebo. Participants and study investigators and personnel were masked to study group assignment. Participants were followed-up for 5 years by primary-care physicians and in expert memory centres. The primary outcome was conversion to probable Alzheimer's disease in participants who received at least one dose of study drug or placebo, compared by use of the log-rank test. This study is registered with ClinicalTrials.gov, number NCT00276510.

Findings Between March, 2002, and November, 2004, we enrolled and randomly allocated 2854 participants, of whom 1406 received at least one dose of ginkgo biloba extract and 1414 received at least one dose of placebo. By 5 years, 61 participants in the ginkgo group had been diagnosed with probable Alzheimer's disease (1·2 cases per 100 person-years) compared with 73 participants in the placebo group (1·4 cases per 100 person-years; hazard ratio [HR] 0·84, 95% CI 0·60–1·18; p=0·306), but the risk was not proportional over time. Incidence of adverse events was much the same between groups. 76 participants in the ginkgo group died compared with 82 participants in the placebo group (0·94, 0·69–1·28; p=0·68). 65 participants in the ginkgo group had a stroke compared with 60 participants in the placebo group (risk ratio 1·12, 95% CI 0·77–1·63; p=0·57). Incidence of other haemorrhagic or cardiovascular events also did not differ between groups.

Interpretation Long-term use of standardised ginkgo biloba extract in this trial did not reduce the risk of progression to Alzheimer's disease compared with placebo.

Lancet Neurol 2012; 11: 851–59

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See **Comment** page 836

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IOS Press

Homotaurine Effects on Hippocampal Volume Loss and Episodic Memory in Amnestic Mild Cognitive Impairment

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Accepted 5 November 2015

Abstract. Homotaurine supplementation may have a positive effect on early Alzheimer's disease. Here, we investigated its potential neuroprotective effect on the hippocampus structure and episodic memory performances on amnestic mild cognitive impairment (aMCI). Neuropsychological, clinical, and neuroimaging assessment in 11 treated and 22 untreated patients were performed at baseline and after 1 y. Magnetic resonance data were analyzed using voxel-based morphometry to explore significant differences (Family Wise Error corrected) between the two groups over time. Patients treated with homotaurine showed decreased volume loss in the left and right hippocampal tail, left and right fusiform gyrus, and right inferior temporal cortex which was associated with improved short-term episodic memory performance as measured by the recency effect of the Rey 15-word list learning test immediate recall. Thus, homotaurine supplementation in individuals with aMCI has a positive effect on hippocampus atrophy and episodic memory loss. Future studies should further clarify the mechanisms of its effects on brain morphometry.

Keywords: Amnestic mild cognitive impairment, episodic memory, hippocampus, homotaurine, structural magnetic resonance imaging, tramiprosate

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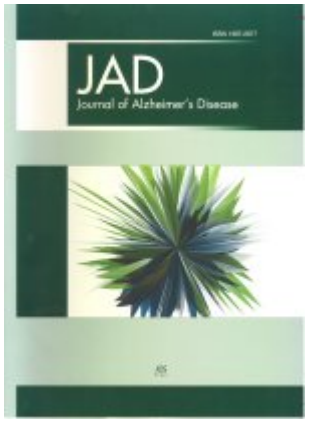


Review

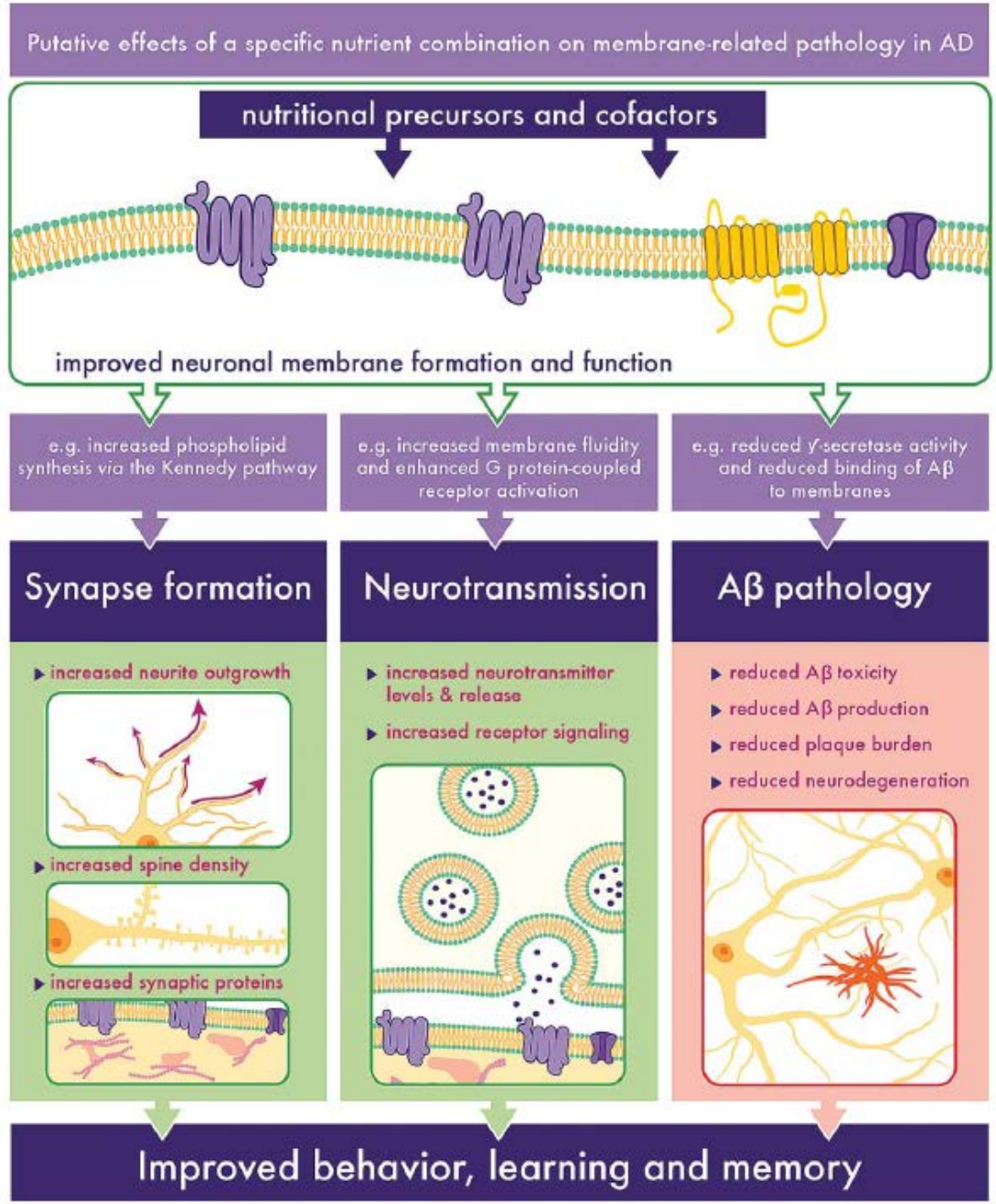
Targeting Synaptic Dysfunction in Alzheimer's Disease by Administering a Specific Nutrient Combination

Nick van Wijk[a,*], Laus M. Broersen[a], Martijn C. de Wilde[a], Robert J.J. Hageman[a], Martine Groenendijk[a], John W.C. Sijben[a] and Patrick J.G.H. Kamphuis[a,b]

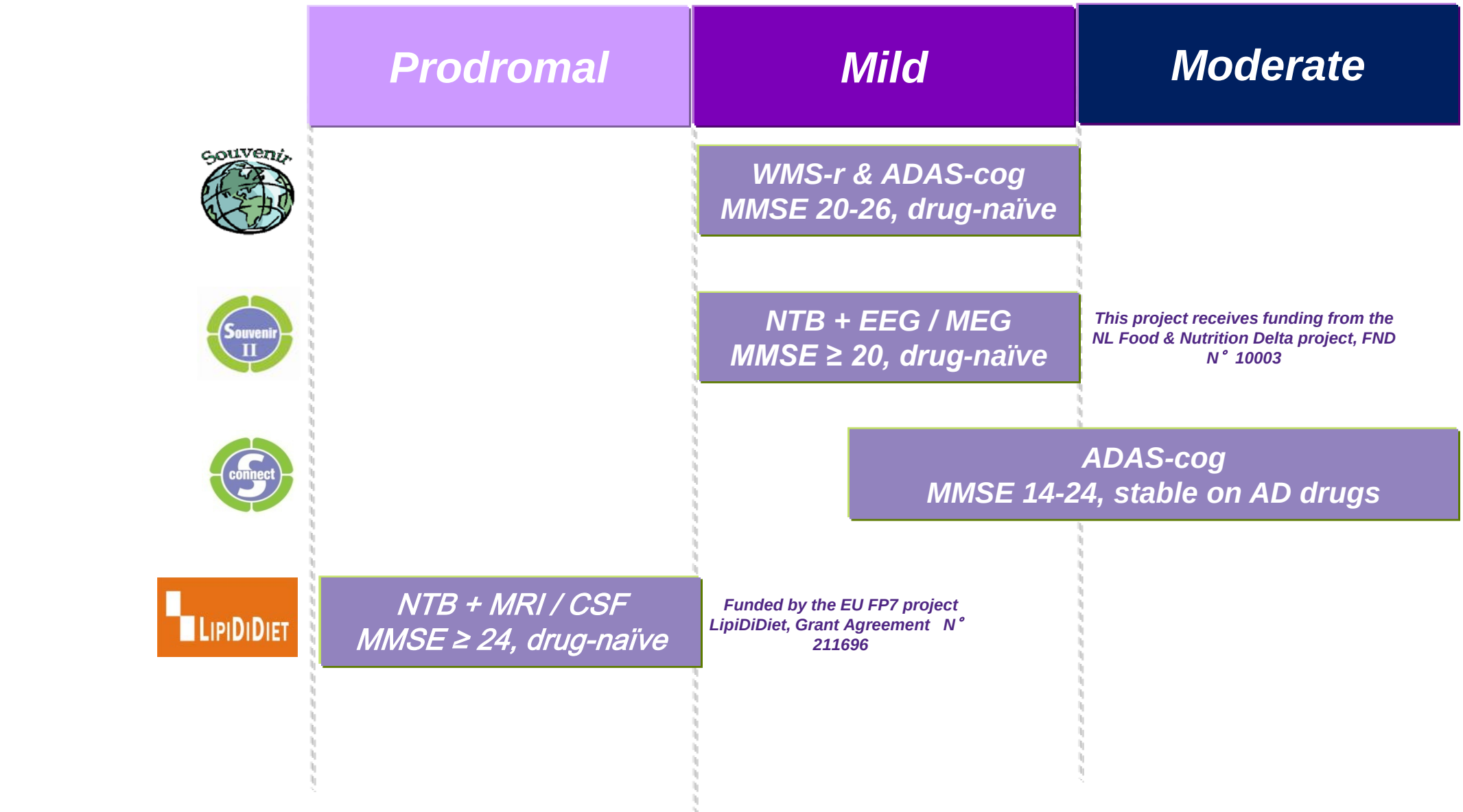
Journal of Alzheimer's Disease 38 (2014) 459–479

Fortasyn™ Connect PATENTED

- **Uridine (UMP): 625 mg**
- **Omega-3 fatty acids: EPA 1200 mg, DHA 300 mg**
- **Choline: 400 mg**
- **Phospholipids: 106 mg**
- **B vitamins: folic acid 400 mcg, Vit B6 1 mg, Vit B12 3 mcg**
- **Antioxidants:, Vit C 80 mg, Vit E 40 mg, Selenium 60 mcg**



Full clinical trial programme across the Ad spectrum



Journal of Alzheimer's Disease 55 (2017) 1131–1139
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IOS Press

Effect Size Analyses of Souvenaid in Patients with Alzheimer's Disease

Jeffrey Cummings[a,*], Philip Scheltens[b], Ian McKeith[c], Rafael Blesa[d], John E. Harrison[b,e], Paulo H.F. Bertolucci[f], Kenneth Rockwood[g,h,i,j], David Wilkinson[k], Wouter Wijker[l], David A. Bennett[m] and Raj C. Shah[n]

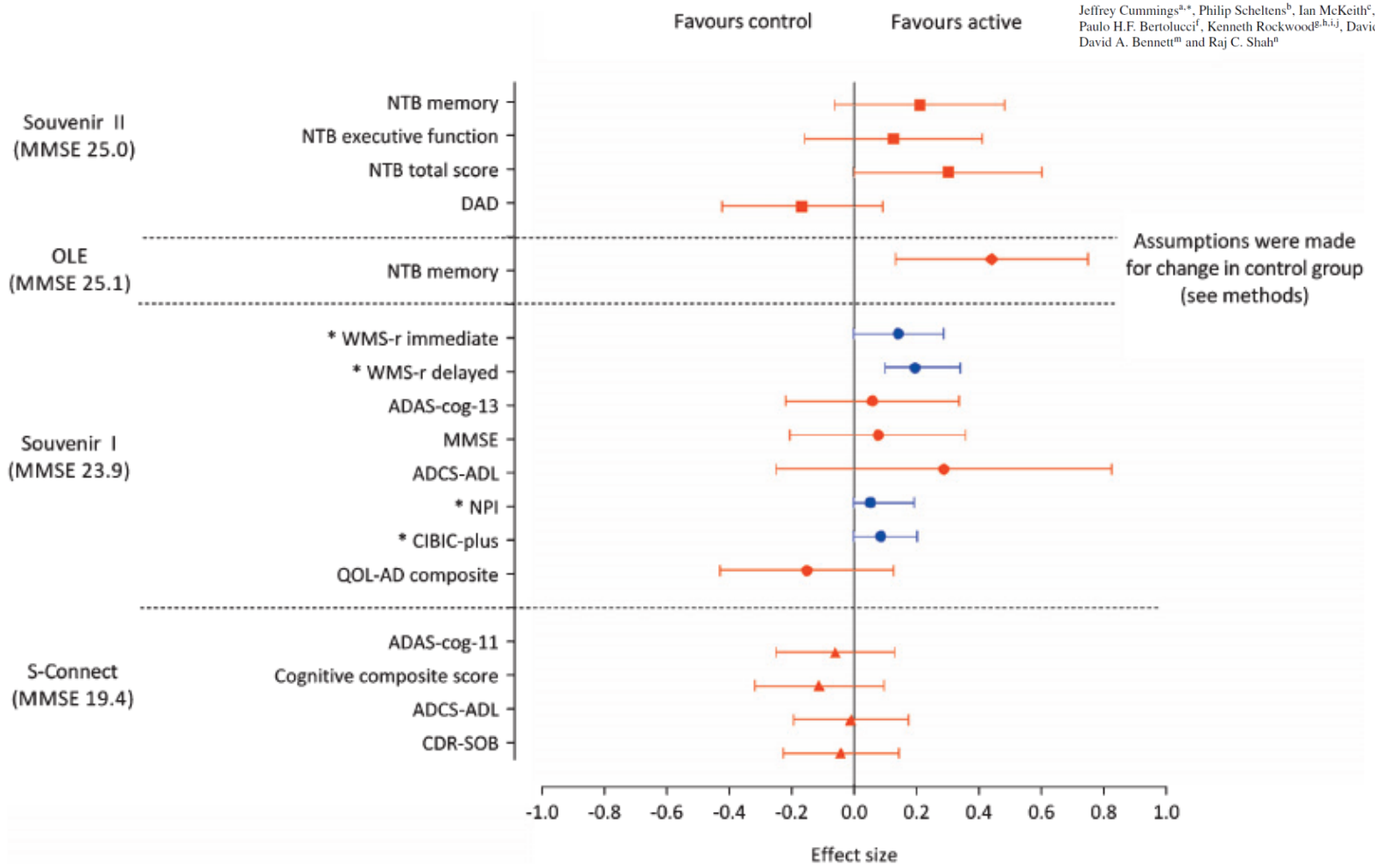


Fig. 1. Effect sizes (point estimate and 95% CI) for the main primary and secondary outcome measures in the Souvenir I (●), Souvenir II (■), open-label extension (OLE) (♦), and S-Connect (▲) studies in patients with mild and mild to moderate Alzheimer's disease. Mean baseline values of the Mini-Mental State Examination (MMSE) score of the total study populations are shown in the figure. Effect sizes were calculated using Cohen's *d* [18] (red) for change from baseline values, except for CIBIC-plus (values at week 12 were used), and Cramér's V [19] (blue) for nominal data. Cohen's *d* values range from $-\infty$ to $+\infty$, with a positive effect size indicating improvement in the active (Souvenaid) group versus control and vice versa. Cramér's V values range from 0 (no association) to 1 (perfect association).

Efficacy of Souvenaid in mild Alzheimer's disease: summary of the results from RCTs

- RCT demonstrated that the supplementation for 12/24 with a multi-nutrient product improves memory deficit in mild AD patients
- Very mild subjects showed better results
- OLE confirmed sintomatic effect on memory domains

La risposta al trattamento si correla in modo significativo con la durata del trattamento (r=0.246; p=.001; fig A) e con i valori del MMSE alla baseline (r=.169; p=.0001; fig. B).

Fig A

Mesi di trattamento con Souvenaid

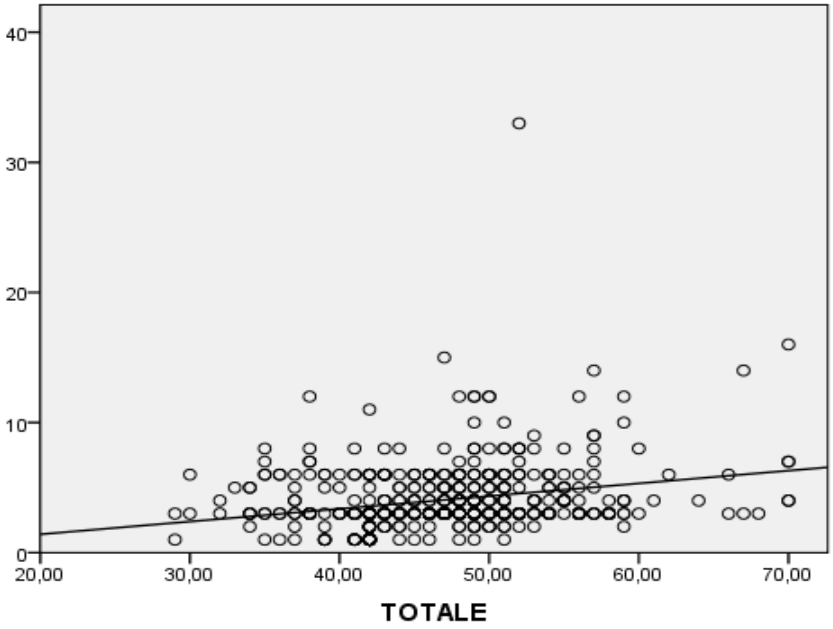
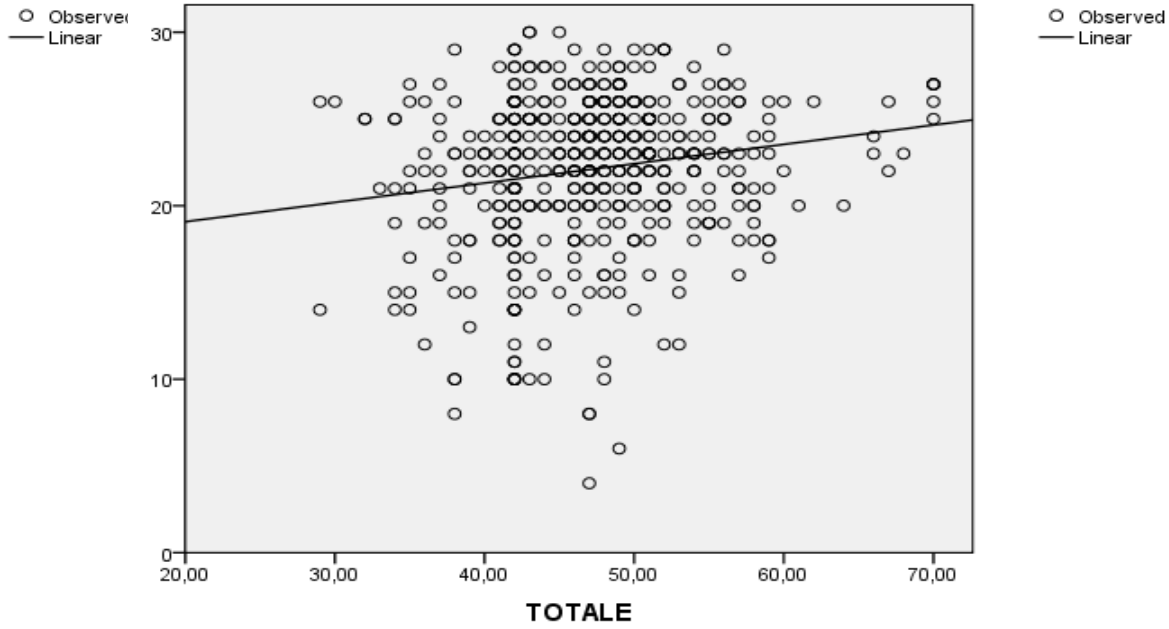


Fig B

Punteggio MMSE



Souvenaid
NUTRICIA
Progetto Memento

24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial

*Hilkka Soininen, Alina Solomon, Pieter Jelle Visser, Suzanne B Hendrix, Kaj Blennow, Miia Kivipelto, Tobias Hartmann, on behalf of the LipiDiDiet clinical study group**

Summary

Background Nutrition is an important modifiable risk factor in Alzheimer's disease. Previous trials of the multinutrient Fortasyn Connect showed benefits in mild Alzheimer's disease dementia. LipiDiDiet investigated the effects of Fortasyn Connect on cognition and related measures in prodromal Alzheimer's disease. Here, we report the 24-month results of the trial.

Methods LipiDiDiet was a 24-month randomised, controlled, double-blind, parallel-group, multicentre trial (11 sites in Finland, Germany, the Netherlands, and Sweden), with optional 12-month double-blind extensions. The trial enrolled individuals with prodromal Alzheimer's disease, defined according to the International Working Group (IWG)-1 criteria. Participants were randomly assigned (1:1) to active product (125 mL once-a-day drink containing Fortasyn Connect) or control product. Randomisation was computer-generated centrally in blocks of four, stratified by site. All study personnel and participants were masked to treatment assignment. The primary endpoint was change in a neuropsychological test battery (NTB) score. Analysis was by modified intention to treat. Safety analyses included all participants who consumed at least one study product dose. This trial is registered with the Dutch Trial Register, number NTR1705.

Findings Between April 20, 2009, and July 3, 2013, 311 of 382 participants screened were randomly assigned to the active group (n=153) or control group (n=158). Mean change in NTB primary endpoint was –0·028 (SD 0·453) in the active group and –0·108 (0·528) in the control group; estimated mean treatment difference was 0·098 (95% CI –0·041 to 0·237; p=0·166). The decline in the control group was less than the prestudy estimate of –0·4 during 24 months. 66 (21%) participants dropped out of the study. Serious adverse events occurred in 34 (22%) participants in the active group and 30 (19%) in control group (p=0·487), none of which were regarded as related to the study intervention.

Interpretation The intervention had no significant effect on the NTB primary endpoint over 2 years in prodromal Alzheimer's disease. However, cognitive decline in this population was much lower than expected, rendering the primary endpoint inadequately powered. Group differences on secondary endpoints of disease progression measuring cognition and function and hippocampal atrophy were observed. Further study of nutritional approaches with larger sample sizes, longer duration, or a primary endpoint more sensitive in this pre-dementia population, is needed.

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Lancet Neurol 2017

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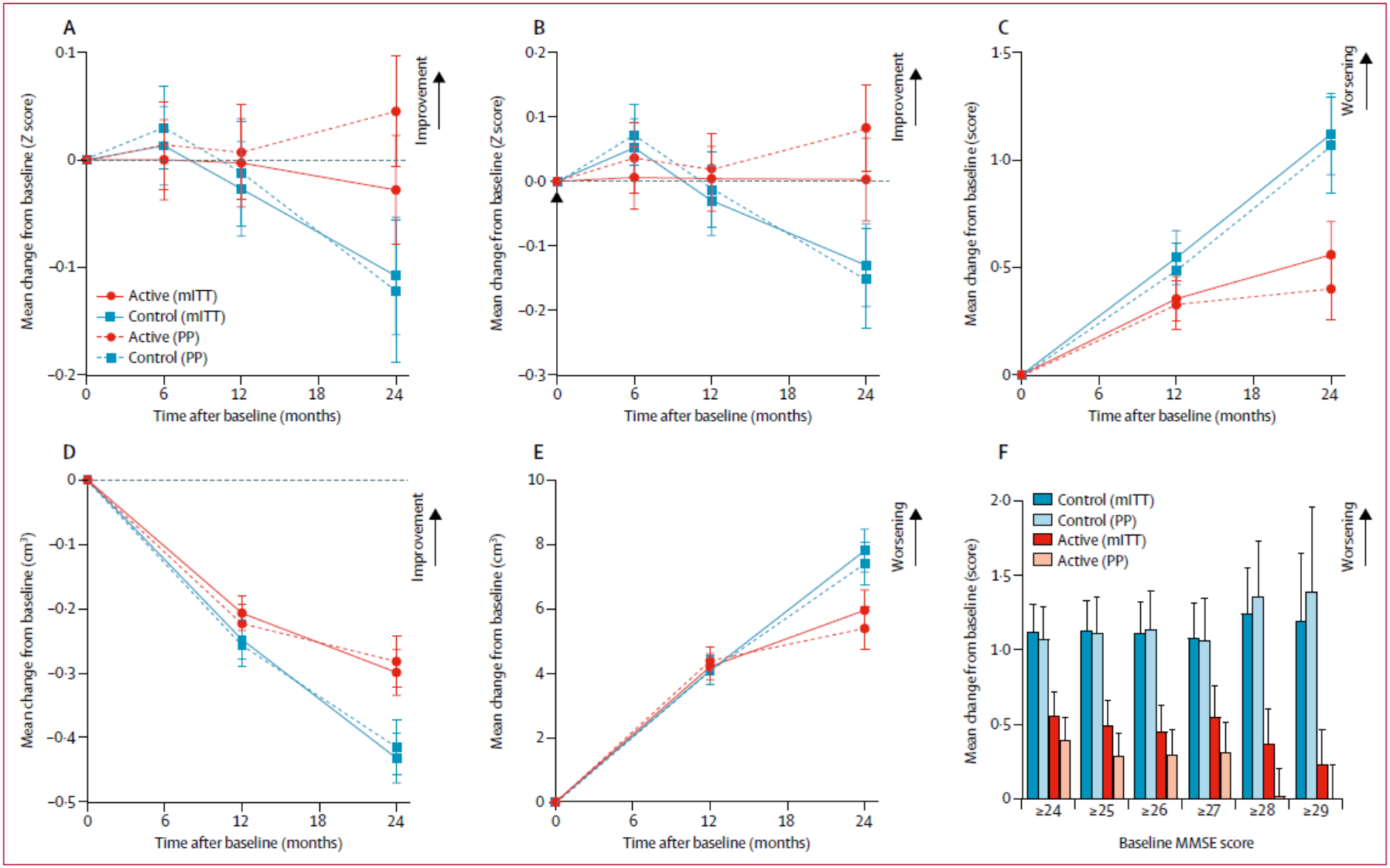

***Figure 2*: Changes in main endpoints during the 24-month intervention**

(A) NTB primary endpoint. (B) NTB memory domain. (C) CDR-SB. (D) MRI total hippocampal volume. (E) MRI ventricular volume. (F) CDR-SB in subgroups defined by baseline MMSE. Data are observed mean change from baseline; error bars are SE. Sample size by baseline MMSE subgroup (control/active): ≥24: mITT 117/106 (PP 96/89), ≥25: 104/91 (86/75), ≥26: 95/79 (78/66), ≥27: 77/63 (66/53), ≥28: 55/43 (48/37), ≥29 29/21 (24/19). CDR-SB=clinical dementia rating-sum of boxes. mITT=modified intention-to-treat analysis. MMSE=Mini-Mental State Examination. NTB=neuropsychological test battery. PP=per-protocol analysis.

NUTRITIONAL APPROACH TO DISEASES

- Nutritional support
  - disease-related malnutrition and reduced protein-calorie intake
- Dietary therapy
  - dietary pattern and nutrient content (protein, lipid, carbohydrate, mineral salt)
- Pharmaconutrition/Medical food
  - specific nutrient to manage a disease or condition that has distinctive nutritional requirements

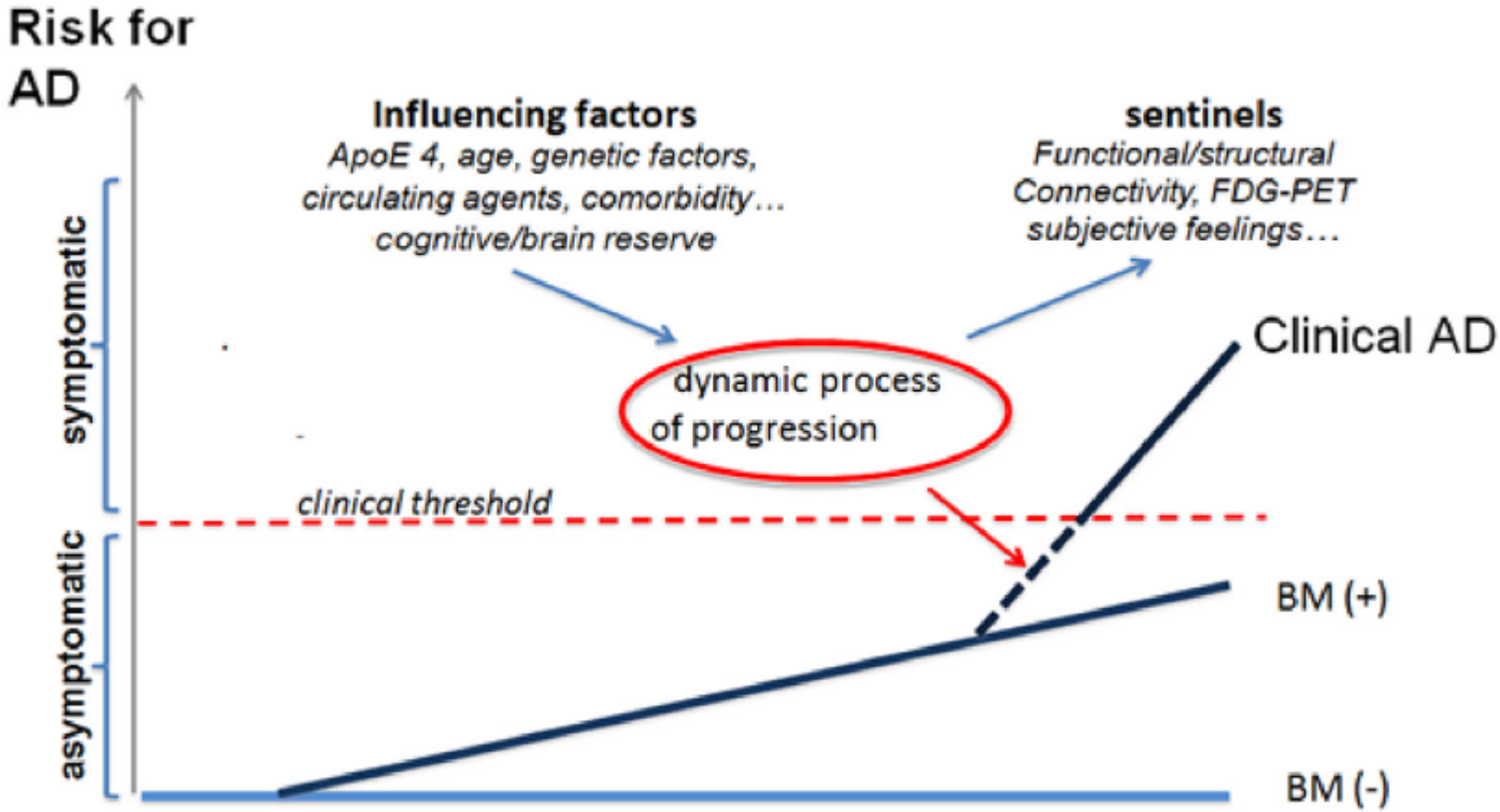

Fig. 2. The risk of clinical AD–hypothetical model. Abbreviation: AD, Alzheimer's disease; BM, pathophysiological biomarkers.